APPROVED DRUG PRODUCTS
with
THERAPEUTIC EQUIVALENCE EVALUATIONS

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This volume is current through December 31, 2000.

21ST EDITION

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFORMATION TECHNOLOGY
DIVISION OF DATA MANAGEMENT AND SERVICES

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1. INTRODUCTION

1.1 Content and Exclusion

The List is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs; (3) drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research; and (4) a cumulative list of approved products that have never been marketed, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. This publication also includes indices of prescription and OTC drug products by trade or established name (if no trade name exists) and by applicant name (holder of the approved application). All established names for active ingredients generally conform to official compendial names or *United States Adopted Names* (USAN) as prescribed in (21 CFR 299.4(e)). The latter list includes applicants' names as abbreviated in this publication; in addition, a list of uniform terms is provided. An *Addendum* contains drug patent and exclusivity information for the Prescription and OTC Drug Product Lists, and for the Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research.

This publication also includes additional information, such as Orphan Drug Product Designations and other data that the Agency deems appropriate to disseminate.

Prior to the 6th Edition, the publication had excluded OTC drug products and drug products with approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research because the main purpose of the publication was to provide information to states regarding FDA's recommendation as to which generic prescription drug products were acceptable candidates for drug product selection. The 1984 Amendments required the Agency to begin publishing an up-to-date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required.

Under the 1984 Amendments, some drug products were given tentative approvals. Prior to the effective date, the Agency will not include drug products with tentative approval in the List; however, they are available in the *FDA Drug Product Approvals List* on the Internet World Wide Web. When the tentative approval becomes a full approval through a subsequent action letter to the application holder, the Agency will list the drug product and the final, effective approval date in the appropriate approved drug product list.

Distributors or repackagers of products on the List are not identified. Because distributors or repackagers are not required to notify FDA when they shift their sources of supply from one approved manufacturer to another, it is not possible to maintain complete information linking product approval with the distributor or repackager handling the products.

1.2 Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics

such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., propoxyphene hydrochloride vs. pentazocine hydrochloride for the treatment of pain).* Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications.

FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Bioavailability. This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalent Drug Products. This term describes pharmaceutical equivalent or pharamaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(7)(B) of the Act describes one set of conditions under which a test and reference listed drug (see Section 1.4) shall be considered bioequivalent:

> the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
>
> the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

1.3 Statistical Criteria for Bioequivalence

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent drug products are therapeutically equivalent, and therefore, interchangeable.

Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action (Federal Food, Drug and Cosmetic Act, section 505(j)(8)). Bioequivalence refers to equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations. Underlying the concept of bioequivalence is the thesis that, if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product. Methods used to define bioequivalence can be found in 21 CFR 320.24, and include (1) pharmacokinetic (PK) studies, (2) pharmacodynamic (PD) studies, (3) comparative clinical trials, and (4) in-vitro studies. The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

The standard bioequivalence (PK) study is conducted using a two-treatment crossover study design in a limited number of volunteers, usually 24 to 36 adults. Alternately, a four-period, replicate design crossover study may also be used. Single doses of the test and reference drug products are administered and blood or plasma levels of the drug are measured over time. Pharmacokinetic parameters

characterizing rate and extent of drug absorption are evaluated statistically. The PK parameters of interest are the resulting area under the plasma concentration-time curve (AUC), calculated to the last measured concentration ($AUC_{(0-t)}$) and extrapolated to infinity ($AUC_{(0-inf)}$), for extent of absorption; and the maximum or peak drug concentrations (Cmax), for rate of absorption. Crossover studies may not be practical in drugs with a long half-life in the body, and a parallel study design may be used instead. Alternate study methods, such as in-vitro studies or equivalence studies with clinical or pharmacodynamic endpoints, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays and topical products applied to the skin).

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products. Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC). The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative in-vitro methodology.

The bioequivalence methodology and criteria described above simultaneously control for both, differences in the average response between test and reference, as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and Cmax) of the two products and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study. A test product with no differences in the average response when compared to the reference might still fail to pass the bioequivalence criteria if the variability of one or both products is high and the bioequivalence study has insufficient statistical power (i.e., insufficient number of subjects). Likewise, a test product with low variability may pass the bioequivalence criteria, when there are somewhat larger differences in the average response.

This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product. The Office of Generic Drugs has conducted two surveys to quantify the differences between generic and brand name products. The first survey included 224 bioequivalence studies submitted in approved applications during 1985 and 1986. The observed average differences between reference and generic products for AUC was 3.5% (JAMA, Sept. 4, 1987, Vol. 258, No. 9). The second survey included 127 bioequivalence studies submitted to the agency in 273 ANDAs approved in 1997.

The three measures reviewed include $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and Cmax. The observed average differences between the reference and generic products were ± 3.47% (SD 2.84) for $AUC_{(0-t)}$, ± 3.25% (SD 2.97) for $AUC_{(0-inf)}$, and ± 4.29% (SD 3.72) for Cmax (JAMA, Dec. 1, 1999, Vol. 282, No. 21).

The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice of carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent to the reference will be approved.

1.4 Reference Listed Drug

A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared. By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when multiple NDAs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of an NDA listed drug that is not designated as the reference listed may petition the Agency through the Citizen Petition procedure (see 21 CFR 10.25(a) and CFR 10.30). When the Citizen Petition is approved, the second NDA will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug. Section 1.7, *Therapeutic Equivalence Evaluations Codes — Products meeting necessary bioequivalence requirements* explains the ***(AB, AB1, AB2, AB3***... coding system for multisource drug products listed under the same heading with two reference listed drugs.

In addition, there are two situations in which two NDA drug products that have been shown to be bioequivalent to each other may both be designated as reference listed drugs. The first situation occurs when the *in vivo* determination of bioequivalence is self-evident and a waiver of the *in vivo* bioequivalence may be granted. The second situation occurs when the bioequivalence of two NDA drug products may be determined through *in vitro* methodology. The reference listed drug is identified by the symbol "+" in the Prescription and Over-the Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics, otics, and topical products. It is recommended that a firm planning to conduct an *in vivo* bioequivalence study, or planning to manufacture a batch of a drug product for which an *in vivo* waiver of bioequivalence will be requested, contact the Division of Bioequivalence, Office of Generic Drugs, to confirm the appropriate reference listed drug.

Acyclovir 200MG Tablet-Reference Listed. Novopharm's single source acyclovir tablets have been declared to be a reference listed drug for the 200 mg tablet in addition to the acylcovir (Zovirax) 800 mg tablet of the innovator. A generic firm wishing to submit an ANDA for a duplicate of the 200 mg acyclovir tablet will be eligible for a waiver of the *in vivo* determination of bioequivalence (1) if their product is proportionally similar in its active and inactive ingredients to their own 800 mg acyclovir tablet and (2) by doing an acceptable comparative dissolution

test (dissolution profile) against Novopharm's 200 mg acyclovir reference listed drug.

Before a waiver of the *in vivo* determination of bioequivalence can be granted for the 200 mg acyclovir tablet, the generic firm must have completed an acceptable fasting and fed study comparing their acyclovir 800 mg tablet against the Zovirax 800 mg tablet.

For further information on the study designs, you should contact the Division of Bioequivalence, Office of Generic Drugs.

1.5 General Policies and Legal Status

The List contains public information and advice. It does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalence of drug products that have been approved, it contains FDA's advice to the public, to practitioners and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers. To the extent that the List identifies drug products approved under Section 505 of the Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act. Exclusion of a drug product from the List does not necessarily mean that the drug product is either in violation of Section 505 of the Act, or that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

1.6 Practitioner/User Responsibilities

Professional care and judgment should be exercised in using the List. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Multisource and single-source drug products. FDA has evaluated for therapeutic equivalence only multisource prescription drug products, which in most instances means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence code is included and, in addition, product information is highlighted in bold face and underlined. Those products with approved applications that are single-source (i.e., there is only one approved product available for that active ingredient, dosage form and route of administration) are also included on the List, but no therapeutic equivalence code is included with such products. Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, although not identified in the List, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. The details of these codes and the policies underlying them are discussed in Section 1.7, *Therapeutic Equivalence Evaluations Codes*.

Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product. The applicant may have had its product manufactured by a contract manufacturer and may simply be distributing the product for which it has obtained approval. In most instances, however, the manufacturer of the product is also the applicant. The name of the manufacturer is permitted by regulation to appear on the label, even when the manufacturer is not the marketer.

Although the products on the List are identified by the names of the applicants, circumstances, such as changing corporate ownership, have sometimes made identification of the applicant difficult. The Agency believes, based on continuing document review and communication with firms, that the applicant designations on the List are, in most cases, correct.

To relate firm name information on a product label to that on the List, the following should be noted: the applicant's name always appears on the List. This applies whether the applicant (firm name on the Form FDA 356h in the application) is the marketer (firm name in largest letters on the label) or not. However, the applicant's name may not always appear on the label of the product.

If the applicant is the marketer, its name appears on the List and on the label; if the applicant is not the marketer, and the Agency is aware of a corporate relationship (e.g., parent and subsidiary) between the applicant and the marketer, the name of the applicant appears on the List and both firm names may appear on the label. Firms with known corporate relationships are displayed in Appendix B. If there is no known corporate relationship between the applicant and the marketer, the applicant's name appears on the List; however, unless the applicant is the manufacturer, packager, or distributor, the applicant's name may not appear on the label. In this case, the practitioner, from labeling alone, will not be able to relate the marketed product to an applicant cited in the List, and hence to a specific approved drug product. In such cases, to assure that the product in question is the subject of an approved application, the firm named on the label should be contacted.

To relate trade name (proprietary name) information on a product label to that on the List, the following should be noted: if the applicant is the marketer, its name appears on the List and on the label; if the Agency is aware of a corporate relationship between the applicant and the marketer, the trade name (proprietary name) of the drug product (established drug name if no trade name exists) appears on the List. If a corporate relationship exists between an application holder and a marketer and both firms are distributing the drug product, the FDA reserves the right to select the trade name of either the marketer or the application holder to appear on the List. If there is no known corporate relationship between the applicant and the marketer, the established drug name appears on the List.

Every product on the List is subject at all times to regulatory action. From time to time, approved products may be found in violation of one or more provisions

of the Act. In such circumstances, the Agency will commence appropriate enforcement action to correct the violation, if necessary, by securing removal of the product from the market by voluntary recall, seizure, or other enforcement actions. Such regulatory actions are, however, independent of the inclusion of a product on the List. The main criterion for inclusion of a product is that it has an application with an effective approval that has not been withdrawn for safety or efficacy reasons. FDA believes that retention of a violative product on the List will not have any significant adverse health consequences, because other legal mechanisms are available to the Agency to prevent the product's actual marketing. FDA may however, change a product's therapeutic equivalence rating if the circumstances giving rise to the violation change or otherwise call into question the data upon which the Agency's assessment of whether a product meets the criteria for therapeutic equivalence was made.

1.7 Therapeutic Equivalence Evaluations Codes

The coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With few exceptions, the therapeutic equivalence evaluation date is the same as the approval date.

The two basic categories into which multisource drugs have been placed are indicated by the first letter as follows:

A — Drug products that FDA considers to be <u>therapeutically equivalent</u> to other pharmaceutically equivalent products, i.e., drug products for which:

(1) there are no known or suspected bioequivalence problems. These are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form; or

(2) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. These are designated **AB**.

B — Drug products that FDA at this time, considers <u>not to be therapeutically equivalent</u> to other pharmaceutically equivalent products, i.e.,

drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated **BC**, **BD**, **BE**, **BN**, **BP**, **BR**, **BS**, **BT**, **BX**, or **B***.

Individual drug products have been evaluated as therapeutically equivalent to the reference product in accordance with the definitions and policies outlined below:

"A" CODES

Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.

"**A**" products are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. Drug products designated with an "**A**" code fall under one of two main policies:

(1) for those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied for solid oral dosage forms by a showing that an acceptable *in vitro* dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form, as described below); or

(2) for those DESI drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product (these products are designated as **AB**).

There are some general principles that may affect the substitution of pharmaceutically equivalent products in specific cases. Prescribers and dispensers of drugs should be alert to these principles so as to deal appropriately with situations that require professional judgment and discretion.

There may be labeling differences among pharmaceutically equivalent products that require attention on the part of the health professional. For example, pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary with respect to their expiration time or storage conditions after reconstitution. An FDA evaluation that such products are therapeutically equivalent is applicable only when each product is reconstituted, stored, and used under the conditions specified in the labeling of that product.

The Agency will use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and otherwise therapeutically equivalent, when they should be brought to the attention of health professionals. These notes are contained in Section 1.8, *Description of Special Situations*.

For example, in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to Section 1.8.

Also, occasionally a situation may arise in which changes in a listed drug product after its approval (for example, a change in dosing interval) may have an impact on the substitutability of already approved generic versions of that product that were rated by the Agency as therapeutically equivalent to the listed product. When such changes in the listed drug product are considered by the Agency to have a significant impact on therapeutic equivalence, the Agency will change the therapeutic equivalence ratings for other versions of the drug product unless the manufacturers of those other versions of the product provide additional information to assure equivalence under the changed conditions. Pending receipt of the

additional data, the Agency may add a note to Section 1.8, or, in rare cases, may even change the therapeutic equivalence rating.

In some cases (e.g., Isolyte® S w/ Dextrose 5% in Plastic Container and Plasma-Lyte® 148 and Dextrose 5% in Plastic Container), closely related products are listed as containing the same active ingredients, but in somewhat different amounts. In determining which of these products are pharmaceutically equivalent, the Agency has considered products to be pharmaceutically equivalent with labeled strengths of an ingredient that do not vary by more than 1%.

Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. For the purpose of this publication, such products are not considered to be therapeutically equivalent. There are no instances in this List where pharmaceutical alternatives are evaluated or coded with regard to therapeutic equivalence. Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

The codes in this book are not intended to preclude health care professionals from converting pharmaceutically different concentrations into pharmaceutical equivalents using accepted professional practice.

Where package size variations have therapeutic implications, products so packaged have not been considered pharmaceutically equivalent. For example, some oral contraceptives are supplied in 21-tablet and 28-tablet packets; the 28-tablet packets contain 7 placebo or iron tablets. These two packaging configurations are not regarded as pharmaceutically equivalent; thus, they are not designated as therapeutically equivalent.

Preservatives may differ among some therapeutically equivalent drug products. Differences in preservatives and other inactive ingredients do not affect FDA's evaluation of therapeutic equivalence except in cases where these components may influence bioequivalence or routes of administration.

The specific sub-codes for those drugs evaluated as therapeutically equivalent and the policies underlying these sub-codes follow:

AA — Products in conventional dosage forms not presenting bioequivalence problems

Products coded as **AA** contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate *in vitro* bioequivalence standard that is acceptable to the Agency in order to be approved.

AB, AB1, AB2, AB3... — Products meeting necessary bioequivalence requirements

Multisource drug products listed under the same heading (i.e., identical active ingredients(s), dosage form, and route(s) of administration) and having the same strength (see Section 1.2, *Therapeutic Equivalence-Related Terms, Pharmaceutical Equivalents)* generally will be coded **AB** if a study is submitted demonstrating bioequivalence.

In certain instances, a number is added to the end of the **AB** code to make a three character code (i.e., **AB1, AB2, AB3, etc.**). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. If a study is submitted that demonstrates bioequivalence to a specific

listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against. For example, Adalat® CC (Miles) and Procardia XL® (Pfizer), extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Once generic drug products deemed by FDA to be bioequivalent to either Adalat® CC or Procardia XL® are approved, Adalat® CC and Procardia XL® would be assigned ratings of **AB1** and **AB2**, respectively. The generic drug products bioequivalent to Adalat® CC would be assigned a rating of **AB1** and those bioequivalent to Procardia XL® would be assigned a rating of **AB2**. (The assignment of an **AB1** or **AB2** rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated either with an **AB** or three-character code or is single source in the List. Drugs coded as **AB** under a heading are considered therapeutically equivalent only to other drugs coded as **AB** under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

AN — Solutions and powders for aerosolization

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded **AN**. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded **BN**, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded **AN** if the bioequivalence standard is based upon *in vivo* methodology, if bioequivalence needs to be demonstrated by *in vivo* methodology then the drug products will be coded **AB**.

AO — Injectable oil solutions

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

AP — Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, *Injectable; Injection*. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are all considered to be pharmaceutically and therapeutically equivalent provided they are designed to produce the same

concentration prior to injection and are similarly labeled. Consistent wit accepted professional practice, it is the responsibility of the prescriber dispenser, or individual administering the product to be familiar with product's labeling to assure that it is given only by the route(s) c administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers ar not included on the List (e.g., dextrose injection 5%, dextrose injection 10% sodium chloride injection 0.9%) since these products are on the market withou FDA approval and the FDA has not published conditions for marketing suc parenteral products under approved NDAs. When packaged in plastic containers however, FDA regulations require approved applications prior to marketing Approval then depends on, among other things, the extent of the availabl safety data involving the specific plastic component of the product. All larg volume parenteral products are manufactured under similar standards, regardles of whether they are packaged in glass or plastic. Thus, FDA has no reason t believe that the packaging container of large volume parenteral drug product that are pharmaceutically equivalent would have any effect on their therapeuti equivalence.

AT — Topical products

There are a variety of topical dosage forms available for dermatologic ophthalmic, otic, rectal, and vaginal administration, including solutions creams, ointments, gels, lotions, pastes, sprays, and suppositories. Eve: though different topical dosage forms may contain the same active ingredien and potency, these dosage forms are not considered pharmaceutically equivalent Therefore, they are not considered therapeutically equivalent. All solution: and DESI drug products containing the same active ingredient in the sam topical dosage form for which a waiver of *in vivo* bioequivalence has bee granted and for which chemistry and manufacturing processes are adequate t demonstrate bioequivalence, are considered therapeutically equivalent and code **AT**. Pharmaceutically equivalent topical products that raise questions o bioequivalence, including all post-1962 non-solution topical drug products, ar coded **AB** when supported by adequate bioequivalence data, and **BT** in the absenc of such data.

"B" CODES

Drug products that FDA, at this time, considers <u>not to be therapeutically equivalent</u> to othe pharmaceutically equivalent products.

"**B**" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem wit specific dosage forms rather than with the active ingredients. Drug products designated with a "**B**" code fall under one of three main policies:

(1) the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bioequivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or

(2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

(3) the drug products are under regulatory review.

The specific coding definitions and policies for the "B" sub-codes are as follows:

B* — Drug products requiring further FDA investigation and review to determine therapeutic equivalence

The code **B*** is assigned to products previously assigned an **A** or **B** code when FDA receives new information that raises a significant question regarding therapeutic equivalence that can be resolved only through further Agency investigation and/or review of data and information submitted by the applicant. The **B*** code signifies that the Agency will take no position regarding the therapeutic equivalence of the product until the Agency completes its investigation and review.

BC — Extended-release dosage forms (capsules, injectables and tablets)

An extended-release dosage form is defined by the official compendia as one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form).

Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded **BC**, while those for which such data are available have been coded **AB**.

BD — Active ingredients and dosage forms with documented bioequivalence problems

The **BD** code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded **AB**.

BE — Delayed-release oral dosage forms

A delayed-release dosage form is defined by the official compendia as one that releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.

Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the Agency considers different delayed-release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products **BE** in the absence of *in vivo* studies showing bioequivalence. If adequate *in vivo* studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded **AB**.

BN — Products in aerosol-nebulizer drug delivery systems

This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the Agency does not consider different metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard.

BP — Active ingredients and dosage forms with potential bioequivalence problems

FDA's bioequivalence regulations (21 CFR 320.33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded **BP** until adequate *in vivo* bioequivalence data are submitted. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded **BP**. Injectable suspensions are subject to bioequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence.

BR — Suppositories or enemas that deliver drugs for systemic absorption

The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if *in vivo* evidence of bioequivalence is available. In those cases where *in vivo* evidence is available, the product is coded **AB**. If such evidence is not available, the products are coded **BR**.

BS — Products having drug standard deficiencies

If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded **BS**. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded **BS**.

BT — Topical products with bioequivalence issues

This code applies mainly to post-1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance, but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence, will be coded **BT**.

BX — Drug products for which the data are insufficient to determine therapeutic equivalence

The code **BX** is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.

1.8 Description of Special Situations

Certain drugs present special situations that deserve a more complete explanation than can be provided by the two-letter codes used in the List. These drugs have particular problems with standards of identity, analytical methodology, or bioequivalence that are in the process of resolution. The following drugs are in this category:

Amino Acid and Protein Hydrolysate Injections. These products differ in the amount and kinds of amino acids they contain and, therefore, are not considered pharmaceutical equivalents. For this reason, these products are not considered therapeutically equivalent. At the same time, the Agency believes that it is appropriate to point out that where nitrogen balance is the sole therapeutic objective and individual amino acid content is not a consideration, pharmaceutical alternatives with the same total amount of nitrogen content may be considered therapeutically equivalent.

Diclofenac Sodium Ophthalmic Solution 0.1%. Two NDAs have been approved for diclofenac sodium ophthalmic solution 0.1% (DSOS), (1) Ciba's NDA 20-037 for Voltaren and (2) Falcon Pharms' (Alcon) NDA 20-809 for DSOS. Alcon was required to do a study comparing their DSOS to Voltaren and to a placebo control in post cataract surgical inflammation. This study was necessary to demonstrate that the different formulation of the Alcon drug product did not affect the safety and/or effectiveness of the proposed drug product for this indication. Prior to the approval of Alcon's DSOS Ciba did clinical studies and was approved for two additional indications for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery. Three years of Waxman-Hatch marketing exclusivity was granted to Ciba for these two new uses.

Since the treatment of pain has a different site of action than the anti-inflammatory or photophobia indications the Agency did not have information to

support a recommendation that the Alcon and Ciba DSOS are therapeutically equivalent for the treatment of pain. The designation of therapeutic equivalence at this time applies only to the anti-inflammatory indication. The therapeutic equivalence designation will apply to the photophobia indication upon expiration of Ciba's marketing exclusivity.

Ribavirin 200MG Oral Capsule. Indicated for use and comarketed with interferon alfa-2b, recombinant (Intron A), as Rebetron Combination Therapy.

Follitropin Alfa and Beta. Based on available data derived from physico-chemical tests and bioassay, follitropin alfa and follitropin beta are indistinguishable.

Gaviscon®. Gaviscon® is an OTC product which has been marketed since September 1970. The active ingredients in this product, aluminum hydroxide and magnesium trisilicate, were reviewed by the Agency's OTC Antacid Panel and were considered to be safe and effective ingredients (Category I) by that Panel. However, the tablet failed to pass the antacid test which is required of all antacid products. The Agency, therefore, placed the tablet in Category III for lack of effectiveness. A full NDA with clinical studies was submitted by Marion Laboratories, Inc., and approved by FDA on December 9, 1983. Gaviscon® 's activity in treating reflux acidity is made possible by the physical-chemical properties of the inactive ingredients, sodium bicarbonate and alginic acid. Therefore, *all ANDAs which cite Gaviscon® tablets as the listed drug must contain the inactive ingredients sodium bicarbonate and alginic acid.* A full NDA will be required to support the effectiveness of the drug product if different inactive ingredients are to be substituted for sodium bicarbonate or alginic acid or if different proportions of these ingredients are to be used.

1.9 Therapeutic Equivalence Code Change for a Drug Entity

The Agency will use the following procedures when, in response to a petition or on its own initiative, it is considering a change in the therapeutic equivalence code for approved multi-source drug products. Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of drug products in the List (e.g., information concerning the active ingredient or the dosage form), rather than information concerning a single drug product within the category. These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific drug entity and dosage form. The change may be from the code signifying that the drug does not present a bioequivalence problem (e.g., **AA**) to a code signifying a bioequivalence problem (e.g., **BP**), or vice versa. This procedure does not apply to a change of a particular product code (e.g., a change from **BP** to **AB** or from **AB** to **BX**).

Before making a change in a therapeutic equivalence code for an entire category of drugs, the Agency will announce in the *Introduction* to the Cumulative Supplement that it is considering the change, and will invite comment. Comments, along with scientific data, may be sent to the Director, Division of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, (MPN-2) HFD-650, 7500 Standish Place, Rockville, MD 20855. The comment period will generally be 60 days in length, and the closing date for comments will be listed in the description of the proposed change for each drug entity.

The most useful type of scientific data submission is an *in vivo* bioavailability/bioequivalence study conducted on batches of the subject drug products. These submissions should present a full description of the analytical procedures and equipment used, a validation of the analytical methodology, including the standard curve, a description of the method of calculating results, and a description of the pharmacokinetic and statistical models used in analyzing the data. Anecdotal or testimonial information is the least useful to the Agency,

including the standard curve, a description of the method of calculating results, and a description of the pharmacokinetic and statistical models used in analyzing the data. Anecdotal or testimonial information is the least useful to the Agency, and such submissions are discouraged. Copies of supporting reports published in the scientific literature or unpublished material, however, are welcome.

1.10 Change of the Therapeutic Equivalence Evaluation for a Single Product

The aforementioned procedure does not apply to a change in a single drug product code. For example, a change in a single drug product's code from **BP** to **AB** as a result of the submission of a bioequivalence study ordinarily will not be the subject of notice and comment. Likewise, a change in a single drug product's code from **AB** to **BX** (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment. The Agency's responsibility to provide the public with the Agency's most current information related to therapeutic equivalence may require a change in a drug product's code prior to any formal notice and opportunity for the applicant to be heard. The publication in the *Federal Register* of a proposal to withdraw approval of a drug product will ordinarily result in a change in a product's code from **AB** to **BX** if this action has not already been taken.

1.11 Availability of Internal Policy and Procedure Guides

The Office of Generic Drugs maintains internal policy and procedure guides. Although these guides are designed for Office personnel and are subject to change without public notice, they are available to members of the public who may wish to know more about the Office's policies and procedures. Copies of these guides may be obtained from the FDA, Center for Drug Evaluation and Research, HFD-210, Division of Communications Management, Drug Information Branch, 5600 Fishers Lane, Rockville, MD 20857. The Agency welcomes public comment on the policies, procedures, and practices employed in the approval of generic drugs. Such comments may be sent to the Director, Office of Generic Drugs, (MPN-2) HFD-600, 7500 Standish Place, Rockville, MD 20855.

1.12 Discontinued Section

Those drug products in the Discontinued Section of the Orange Book in which a determination has already been made that the products were not marketed or withdrawn for safety or efficacy reasons have been designated by the symbol "*". Those drug products with the symbol "*" are only reflective of citizen petitions approved since 1995.

The identification of these drug products in the Discontinued Section of the Orange Book with the symbol "*" should avoid the submission of multiple citizen petitions for the same drug product.

2. HOW TO USE THE DRUG PRODUCT LISTS

2.1 Key Sections for Using the Drug Product Lists

This publication contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use.

Illustrations. The annotated *Drug Product Illustration,* see Section 2.2, and the *Therapeutic Equivalence Evaluations Illustration,* see Section 2.3, are offered to provide further clarification. These depict the format found in the Prescription Drug Product List (the only list in which therapeutic equivalence evaluation codes are displayed).

Drug Product Lists. The Drug Product Lists, arranged alphabetically by active ingredient, contain product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredient drug products. Also shown are the application number and drug product number (FDA internal computer data use only) and approval dates for those drug products approved on or after January 1, 1982.

If a prescription drug product is available from more than one source (multisource), a therapeutic equivalence code will appear in front of the applicant's name. If a product is therapeutically equivalent to one or more products or to an appropriate reference, it will be designated with a code beginning with **"A"** and the entry will be underlined and printed in bold font for emphasis.

Active ingredient headings for multiple ingredient (combination) drug products are arranged alphabetically. For purposes of this publication, this alphabetical sort takes precedence over United States Pharmacopeia official monograph order (i.e., Reserpine, Hydralazine Hydrochloride, Hydrochlorothiazide). For example, product information labeled as Reserpine, Hydrochlorothiazide and Hydralazine Hydrochloride appears under the active ingredient heading *Hydralazine Hydrochloride; Hydrochlorothiazide; Reserpine.* A cross-reference to the product information (for prescription and OTC products) appears for each additional active ingredient in the product. For combination drug products, the ingredient strengths are separated by semicolons and appear in the same relative sequence as the ingredients in the heading. Available strengths of the dosage form from an applicant appear on separate lines.

To use the Drug Product Lists, determine by alphabetical order the ingredient under which the product information is listed, using the Product Name Index, if necessary. Then, find the ingredient in the applicable Drug Product List. Proceed to the dosage form and route of administration and compare products within that ingredient heading only. Therapeutic equivalence or inequivalence for prescription products is determined on the basis of the therapeutic equivalence codes provided within that specific dosage form heading. The OTC Drug Product List, Discontinued Drug Product List, and Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research List have their data arranged similarly. The Discontinued Drug Product List contains approved products that have never been marketed, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. All products having a "@" in the 12th Cumulative Supplement of the 18th Edition List have been added to the Discontinued Drug Product List appearing in the 19th Edition.

Orphan Drug Product Designations. Drugs and biologicals that have been granted Orphan Designation pursuant to Section 526 as amended by the Orphan Drug Act [P.L. 97-414, January 4, 1983] are listed in Section 3.5.

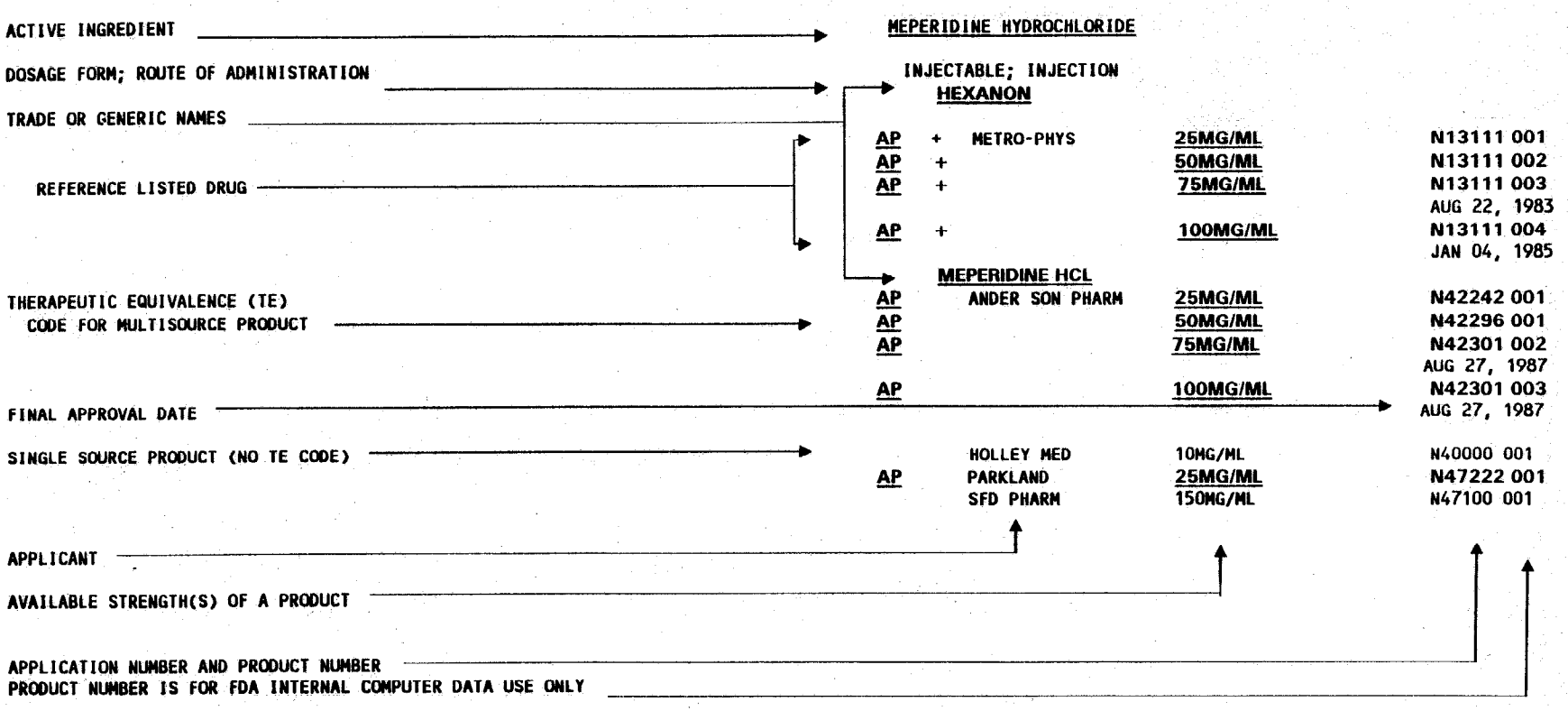
Product Name Index (Prescription and OTC Drug Product Lists). This is an index of drug products by established or trade name. The second term of each entry indicates the active ingredient name under which product information can be found in the appropriate Drug Product List. For those drug products with multiple active ingredients, only the first active ingredient (in alphabetical order) will appear. OTC products are so designated.

Product Name Index Listed by Applicant (Prescription and OTC Drug Product Lists). This is an index that cross-references applicants to drug products. The bolded and underlined entry represents the applicant name abbreviation used in this publication. Each complete applicant name that is represented by the abbreviated name is marked with an asterisk (*). Listed under each complete applicant name is the first alphabetically arranged ingredient under which product information can be found in the appropriate Drug Product List. OTC products are so designated. To use the Drug Product Lists, determine by alphabetical order the ingredient under which the product information is listed, using the Product Name Index, if appropriate.

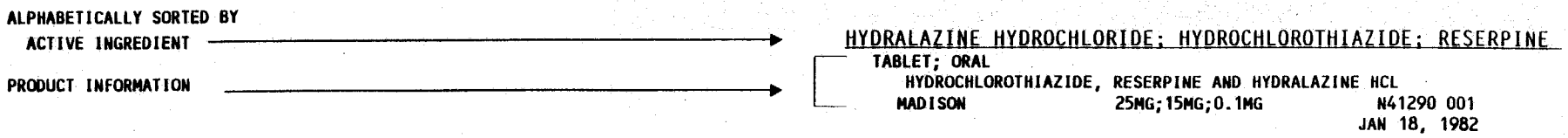
Uniform Terms. To improve readability, uniform terms are used to designate dosage forms, routes of administration, and abbreviations used to express strengths. These terms are listed in Appendix C. In some cases, the terms used may differ from those used in product labels and other labeling.

2.2 DRUG PRODUCT ILLUSTRATION

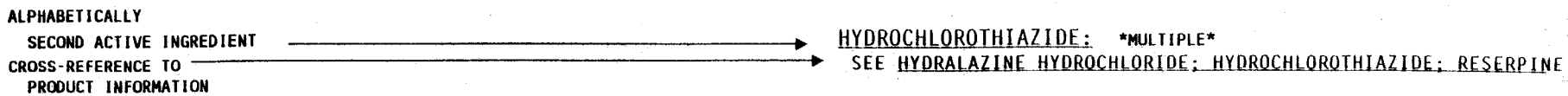
SINGLE INGREDIENT



MULTIPLE INGREDIENTS WITH PRODUCT INFORMATION



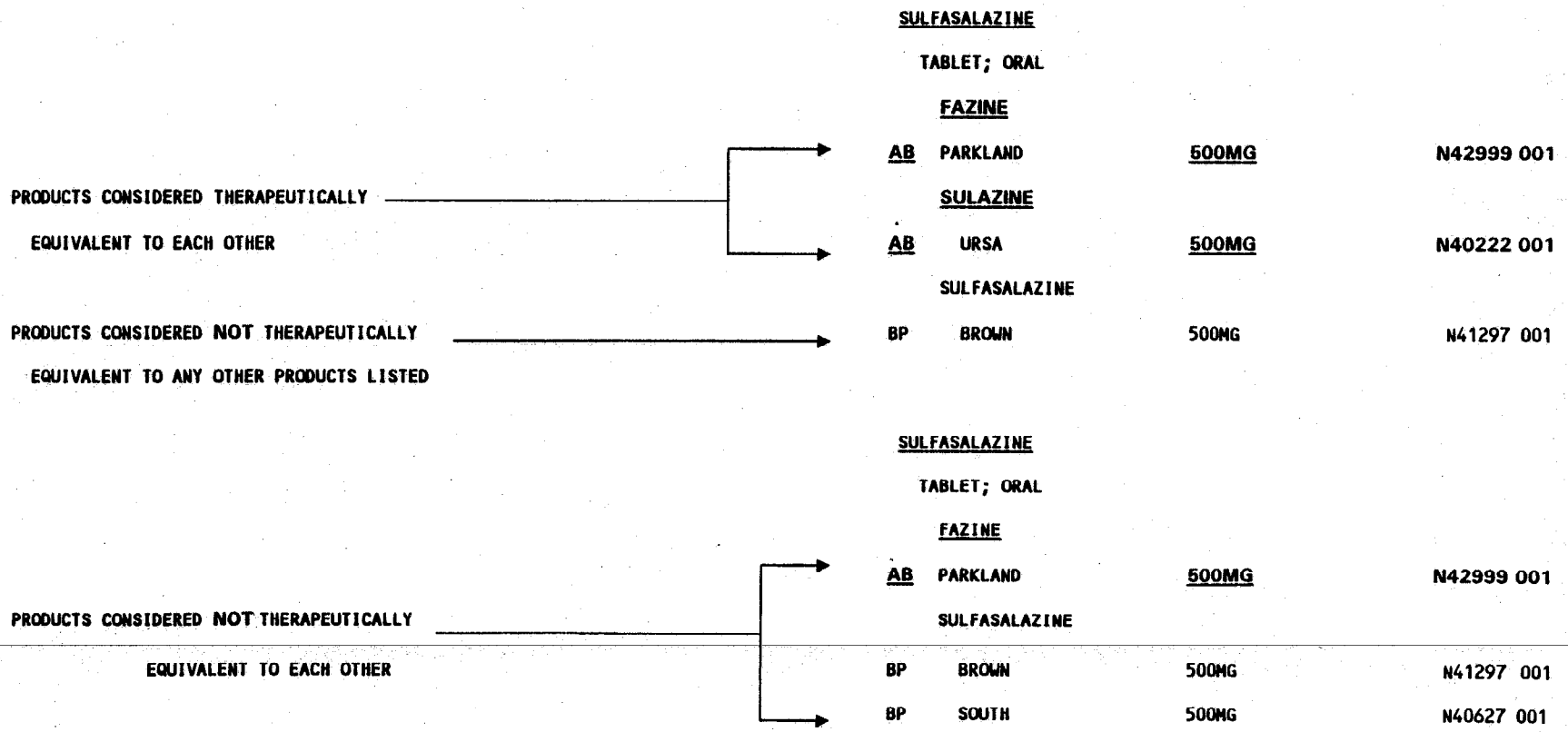
WITH CROSS-REFERENCE



THIS EXAMPLE IS FOR PURPOSES OF ILLUSTRATION ONLY. IT DOES NOT REPRESENT ACTUAL PRODUCTS FROM THE PRESCRIPTION DRUG PRODUCT LIST.

2.3 THERAPEUTIC EQUIVALENCE EVALUATIONS ILLUSTRATION

DRUG PRODUCTS CODED AB (OR ANY CODE BEGINNING WITH AN "A") UNDER AN INGREDIENT AND DOSAGE FORM HEADING ARE CONSIDERED THERAPEUTICALLY EQUIVALENT ONLY TO OTHER PRODUCTS CODED AB (OR ANY CODE BEGINNING WITH AN A") AND NOT TO THOSE CODED BP (OR ANY CODE BEGINNING WITH "B") AND ANY PRODUCTS NOT LISTED. DRUG PRODUCTS CODED BP (OR ANY CODE BEGINNING WITH A "B") ARE NOT CONSIDERED THERAPEUTICALLY EQUIVALENT TO ANY OTHER PRODUCT. FOR A COMPLETE EXPLANATION OF THE TE CODES REFER TO SECTION 1.7 OF THE *INTRODUCTION.*



NOTE: BOLD FONT AND UNDERLINING DENOTES MULTISOURCE PRODUCTS WHICH ARE CONSIDERED THERAPEUTICALLY EQUIVALENT.

THIS EXAMPLE IS FOR PURPOSES OF ILLUSTRATION ONLY. IT DOES NOT REPRESENT ACTUAL PRODUCTS FROM THE PRESCRIPTION DRUG PRODUCT LIST.

PARAMETHADIONE

CAPSULE; ORAL
PARADIONE
ABBOTT 300MG N06800 001

PARICALCITOL

INJECTABLE; INJECTION
ZEMPLAR
+ ABBOTT 0.005MG/ML N20819 001
APR 17, 1998

PAROMOMYCIN SULFATE

CAPSULE; ORAL
HUMATIN
AA + PARKEDALE **EQ 250MG BASE** **N62310 001**
PAROMOMYCIN SULFATE
AA CARACO **EQ 250MG BASE** **N64171 001**
JUN 30, 1997

PAROXETINE HYDROCHLORIDE

SUSPENSION; ORAL
PAXIL
+ SMITHKLINE BEECHAM EQ 10MG BASE/5ML N20710 001
JUN 25, 1997

TABLET; ORAL
PAXIL
SMITHKLINE BEECHAM EQ 10MG BASE N20031 001
DEC 29, 1992
EQ 20MG BASE N20031 002
DEC 29, 1992
EQ 30MG BASE N20031 003
DEC 29, 1992
+ EQ 40MG BASE N20031 005
DEC 29, 1992

TABLET, EXTENDED RELEASE; ORAL
PAXIL CR
+ SMITHKLINE BEECHAM EQ 12.5MG BASE N20936 001
FEB 16, 1999
+ EQ 25MG BASE N20936 002
FEB 16, 1999

PAROXETINE HYDROCHLORIDE

TABLET, EXTENDED RELEASE; ORAL
PAXIL CR
+ SMITHKLINE BEECHAM EQ 37.5MG BASE N20936 003
DEC 06, 2000

PEGADEMASE BOVINE

INJECTABLE; INJECTION
ADAGEN
+ ENZON 250 UNITS/ML N19818 001
MAR 21, 1990

PEMIROLAST POTASSIUM

SOLUTION/DROPS; OPHTHALMIC
ALAMAST
+ SANTEN 0.1% N21079 001
SEP 24, 1999

PEMOLINE

TABLET; ORAL
CYLERT
AB + ABBOTT **18.75MG** **N16832 001**
AB **37.5MG** **N16832 002**
AB + **75MG** **N16832 003**
PEMOLINE
AB AMIDE PHARM **18.75MG** **N75595 001**
FEB 28, 2000
AB **37.5MG** **N75595 002**
FEB 28, 2000
AB **75MG** **N75595 003**
FEB 28, 2000
AB COPLEY PHARM **18.75MG** **N75030 003**
FEB 22, 2000
AB **37.5MG** **N75030 001**
JAN 29, 1999
AB **75MG** **N75030 002**
JAN 29, 1999
AB GENEVA PHARMS TECH **18.75MG** **N75286 001**
DEC 27, 1999
AB **37.5MG** **N75286 002**
JUN 30, 1999